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B. Webb
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE		
	Application Number	09/529,967
	Filing Date	24 April 2000
	First Named Inventor	Matti KORPELA
	Group Art Unit	1655
	Examiner Name	B. Sisson
	Attorney Docket Number	2328-117

Title of the Invention: **TETRACYLINE ASSAY METHOD**

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RULE 132 DECLARATION

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Matti Karp, declare as follows:

1. I am a coinventor of the above-identified application.

2. I received my M.Sc. degree from biochemistry inUniversity of Turku, my Phil Lic. degree from biochemistry in University of Turku and my Ph.D. degree from biochemistry in University of Turku. I have an experience of 20 years dealing with biochemistry of luciferase enzymes and the genes coding for them, as well as their applications and am currently employed as a academy fellow of the Academy of Finland at the Department of Biotechnology, University of Turku, Finland.

3. I have read and understand the Office Action mailed 28 August 2001, in which the Examiner has rejected claims 1-10 and 16-19 under 35 USC §112, first paragraph for lack of enablement. It is the Examiner's position that the present specification is not enabled for the detection of tetracycline in any type of sample regardless of heterogeneity and using any host other than *E. coli* and any vector other than pTetLux1 and pTetLuc1.

4. Techniques for analyzing samples of biological tissues and fluids were well known at the time of the present invention. Any of these techniques can be utilized to analyze such samples and no single technique is essential to the analysis of samples of biological tissues and fluids. Furthermore, techniques for analyzing tetracycline in numerous sample of biological tissues and fluids were well known at the time of the present invention. More specifically, the determination of the tetracycline in these materials, *albeit* by different assay methods, was well known at the time of the present invention. The following represent references which describe testing various samples of biological tissues and fluids for tetracycline.

(a) beef liver, beef kidney, beef muscle, pork liver, pork kidney, pork muscle: Ikai, Y et al., *J. Chromatogr.* (1987) 411:313-323;

(b) beef liver, pork liver, chicken liver, beef muscle, pork muscle, chicken muscle, milk, egg, yellow tail, eel: Oka, H et al., *J. Chromatogr.* (1985) 325: 265-27;

(c) swine urine, swine plasma, swine liver: Sharma, J.P. and Bevill, R.F., *J. Chromatogr.* (1978) 166: 213-220;

(d) sheep urine, sheep plasma, cattle urine, cattle plasma: Sharma, J.P. et al., *J. Chromatogr.* (1977) 134:441-450;

(e) salmon: Carrignan, G. et al., *J. AOAC Int'l*, (1993) 76: 325-328;

(f) milk: Carson, M.C., *J. AOAC Int'l.* (1993) 76:3229-334;

(g) bovine muscle, porcine muscle: Walsh, J.R. et al., *J. Chromatogr.* (1992) 596: 211-216;

(h) cattle muscle, cattle liver, cattle kidney, cattle blood, swine muscle, swine liver, swine kidney, swine blood: Moats, W.A., *J. Chromatogr.* (1986) 358:253-259;

(i) catfish: Moretti, V.M. et al. *Analyst* (1994) 119:2749-2751; and

(j) honey: Oka, H. et al., *J. Chromatogr.* (1987) 400: 253-61.

All of these references clearly demonstrate that tetracycline can be assayed in numerous types of biological samples regardless of heterogeneity. Thus, the isolation and treatment of biological samples, such as from milk, fish, meat, infant formula, eggs, honey, vegetables, serum, plasma or whole blood, to assay for tetracycline requires no undue experimentation.

5. Techniques for preparing recombinant DNA vectors and transfected host cells were well known at the time of the present invention. The Examiner is certainly well aware of the conventional texts in this area, including the following: Maniatis *et al.*, 1982, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY; Sambrook *et al.*, 1989, *Molecular Cloning: A Laboratory Manual*, 2nd Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY; Ausubel *et al.*, 1992, *Current Protocols in Molecular Biology*, J. Wiley and Sons, NY; Glover, 1985, *DNA Cloning*, **I** and **II**, Oxford Press; *Nucleic Acid Hybridization* (B. D. Hames & S. J. Higgins eds. 1984); *Transcription And Translation* (B. D. Hames & S. J. Higgins eds. 1984); B. Perbal, *A Practical Guide To Molecular Cloning* (1984); the treatise, *Methods In Enzymology* (Academic Press, Inc., N.Y.); and *Gene Transfer Vectors For Mammalian Cells*, J. H. Miller and M. P. Calos eds., 1987, Cold Spring Harbor Laboratory. These well known texts describe numerous vectors useful for transfecting numerous host cells, and the well known consideration that any given vector is used for a host in which the vector is capable of replication.

These well known texts also describe numerous expression systems for the production of products of cloned nucleic acids.

6. In addition, the present specification provides sufficient guidance to a person of ordinary skill in the art to practice the claimed invention. The specification clearly describes the components of the vector present in the prokaryotic cells which are used to practice the claimed method. That is, the vector contains a nucleotide sequence which encodes a light-producing enzyme under the transcriptional control of a tetracycline repressor and a tetracycline promoter. Any vector can be used which contains such a nucleotide sequence, and any nucleotide sequence which contains the component parts can be used. The specification further provides guidance that any prokaryotic cell can be used, such as disclosed at page 9, lines 7-17.

7. Furthermore, all of the novel aspects of the invention have been disclosed by the specification. The novel aspect is the use of a prokaryotic cell containing a vector for the determination of tetracycline in a sample. The vector comprises a nucleotide sequence encoding a light producing enzyme under the transcriptional control of a tetracycline repressor and a tetracycline promoter. Each of these elements is known to a skilled artisan. The novel aspect of the gene for a light producing enzyme being under the transcriptional control of a tetracycline repressor and tetracycline promoter is fully disclosed in the specification. Thus, Applicants have supplied the novel aspects of the invention, and the specification does not rely on the knowledge of a skilled artisan to supply any novel aspects.

8. To further demonstrate that the *tet* system was well known to work in other vectors and in other host cells at the time of the present invention, the Examiner's attention is directed to the following references.

(a) *Bacillus subtilis*: Geissendorfer, M. and Hillen, W. (1990), *Appl Microbiol Biotechnol* 33:657-663;

(b) *Schizocaccharomyces pombe*: Faryar, K. and Gatz, C. (1992), *Curr Genet* 21:345-349;

(c) *Saccharomyces cerevisiae*: Dingermann, T. et al. (1992), *EMBO J* 11:1487-1492; Gari, E. et al. (1997), *Yeast* 13:837-848;

(d) *Mus musculus* myoblasts: Hofmann, A. et al. (1996), *Proc Natl Acad Sci USA* 93:5185-5190.

(e) *Mus musculus* brain: Mayford, M et al. (1996), *Science* 274:1678-1683;

(f) eukaryotes: Baron, U. et al. (1997), *Nucl Acids Res* 25:2723-2729; Hermann, B. and Gossen, M. (1998; filing date 1995), U.S. Patent No. 5,814,618; and

(g) *Mus musculus* fibroblasts: Holwell, T.A. et al. (1997), *J Cell Science* 110:1947-1956.

In addition, Rossi F.M.V. and Blau, H.M. (1998), *Curr Opin Biotechnology* 9:451-456 confirms such knowledge in its citation of previous publications (references 1, 2, 4, 5 and 6) showing that the *tet* system was well known to work in other vectors and other hosts. All of these references clearly demonstrate that the *tet* system was well known to work in host cells other than *E. coli* using vectors other than pTetLux1 and pTetLuc1. Thus, the preparation of vectors containing the elements disclosed in the specification, the preparation of host cells containing such vectors and the expression of the construct in such host cells require no undue experimentation.

9. Thus, as clearly demonstrated above, the specification fully enables a person of skill in the art to practice the scope of the rejected claims.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Turku December 19, 2001

Date

Matti Karp